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BACKGROUND

Brain arteriovenous malformations (bAVMs) are abnormal shunts that bypass the capillary bed and directly divert blood from the arterial to the venous circulation, without exchanging nutrients or dissipating the arterial blood pressure. They are thought to be congenital vascular lesions that occur during the late stages of fetal development, however the exact pathogenesis has not been elucidated yet.¹ History of hemorrhage, small AVM size, high arterial feeding blood pressure, and deep venous drainage are the main risk factors that increase the likelihood of AVM rupture. According to the American Stroke Association, 1 in 200-500 people have an AVM, while 25% of AVM patients experience seizures and 50% of patients suffer intracranial hemorrhage (ICH) at some point in their lives.² Also, 5-15% of AVM patients experience severe headaches because of the increased intracranial pressure and a similar percentage of patients exhibit neurological deficits.¹ With the advent of noninvasive imaging, AVMs are being detected at an early, unruptured stage, but the optimal course of action for preventing future complications still remains uncertain. The ARUBA trial strove to determine whether medical management or interventional therapy has a better long-term outcome for patients with unruptured AVMs. While it provides important data, limitations in its study design raise doubts concerning the generalizability of its findings.

The study planned to include 800 patients who were to be followed for a minimum of five and a maximum of seven years.³ They were randomly assigned to one of two groups, the interventional therapy and medical management group. Patients in the medical management group received only pharmacological therapy for the medical symptoms that they experienced (unless they developed hemorrhage or infarction, in which case they were switched into the other group). Patients in the interventional therapy group received endovascular surgery, microsurgery, or radiosurgery, with or without pharmacological therapy depending on their concurrent medical conditions. The primary hypothesis was that medical management is more effective in the treatment of patients with unruptured bAVMs, the primary endpoint was death or stroke, the secondary endpoint was the quality of life, while the functional outcome status was measured using the Rankin scale.³

Previous studies had shown that early interventional treatment in patients with ruptured bAVMs is necessary and patients did not have major future clinical problems.³ Interventional therapy includes endovascular surgery, which aims to occlude the nidus by delivering liquid embolics or embolic coils via a catheter, microsurgical resection of the AVM, or radiosurgery that induces a vascular injury response resulting in AVM obliteration within 1 or 2 years.¹ A multimodal therapy that involves more than one of these interventional procedures can also be performed on certain patients. Furthermore, medical management was shown to be very effective in treating unruptured bAVMs as indicated by the very low rate of future hemorrhage. Yet, based on data from the Columbia University Medical Center, interventional treatment of ruptured AVMs had a significantly greater likelihood of hemorrhage and/or clinical impairment (Rankin score ≥ 2) than medical

management of unruptured AVMs. It is thus imperative to compare the effectiveness of the two methods of treatment only on patients with unruptured bAVMs, since patients who present with an ICH have an already much higher risk of experiencing a subsequent ICH (hazard ratio of 3.6).⁴ The ARUBA trial is the first study comparing medical management to surgical care on patients with unruptured bAVMs and a Rankin score less than two.³

RESULTS

The trial started on April 4, 2007 and ended on April 15, 2013 after following 223 patients for 33 months on average. Both groups had very similar demographics, clinical symptoms, lesion characteristics and modified Rankin scores, with the exception of the interventional therapy group having a slightly higher proportion of small bAVMs (less than 3 cm).⁴ The study ended earlier than planned because it was determined that patients who received interventional therapy had a 3-fold increase in their risk of death or stroke than those who only received pharmacological treatment.⁴ More specifically, 10.1% of patients in the medical management group and 30.7% of patients in the interventional therapy group reached the primary endpoint, stroke or death from any cause during the study.⁵ The primary endpoint incidence rate in the interventional therapy group was found to be very similar to the complication rates of the various invasive procedures when treating bled and unbled brain AVMs: 29% for surgery, 25% for embolization, and 13% for radiotherapy. In contrast, medical management patients had a 2.2% spontaneous rupture rate per year.⁴

The participants of the ARUBA trial will continue to be monitored for at least five more years in order to assess whether the differences observed in the clinical outcome and the Rankin scores will remain the same over time.

DISCUSSION

Brain AVMs can be detected early on while they are unruptured and mostly asymptomatic, but the ideal treatment is still uncertain. The ARUBA trial argues that the best treatment for these patients is solely medical management, using anticonvulsants if the patient has seizures, and analgesics if the patient experiences headaches. However, the ARUBA trial has received plenty of criticism concerning its study design and the credibility of its findings.

The trial states that 30.7% of patients in the interventional treatment group reached the primary endpoint, but the actual symptoms experienced by the patients are not specified. The primary endpoint, stroke, is very broadly defined, including seizure, a new neurological deficit, or headache that results from ischemia or hemorrhage.⁷ There is an obvious difference in the severity of each of these clinical presentations, but the researchers did not identify the likelihood of each symptom based on which interventional treatment the patient received.⁷ Moreover, even though the spontaneous rupture rate per year for patients who undergo medical management is 2.2%, the rate increases with increasing age and patients continue to be at high risk throughout their lives. The complication rates of the various interventional treatments are indeed higher, however, the purpose of interventional therapy is to obliterate the bAVM so that patients can avoid increased risk and be worry-free in the future. Therefore, monitoring patients for only 33 months is inadequate; patients need to be monitored for a few decades in order to assess the risk of hemorrhage throughout their lifespan, as this is imperative information for making the right decision by both the doctor and the patient.⁶

Furthermore, the vast heterogeneity in the bAVM morphology and in the selection of the interventional treatment that the patients received deems

the generalizability of the trial findings questionable. First, there is concern that Mohr et al. introduced selection bias in the study by studying only relatively mild cases of bAVMs, because including only bAVMs without any previous complications is not reflective of the majority of the cases seen in the hospital. Only 13% (226 out of 1740) of the patients screened were selected, but the reasons for excluding the rest were not explicitly stated.⁶ If the actual risk of spontaneous rupture is higher, then conservative medical management may not be sufficient. Additionally, the effectiveness of each interventional method varies drastically based on the bAVM morphology.^{8,9,10} Mohr et al. did not provide enough information concerning the success rate of each procedure used to treat the different bAVM types. More details are needed about the embolic material used in the embolization procedures, the number and outcome of patients with total versus near-total occlusion, and the use of gamma knife versus linear accelerator in radiotherapy.⁷ Lastly, many consider microsurgical resection of bAVMs to be more effective than embolization and radiosurgery in obliterating the nidus, yet it was used on very few patients. It was the only treatment used in 5% of the patients and used in combination with another procedure in 13% of the patients, but the reasons behind the preferential use of the other two methods over microsurgical resection were not explained.^{6,7}

Due to these limitations in the ARUBA trial, it is questionable whether we can group all of the interventional methods together when assessing their effectiveness in curing bAVMs in comparison to medical management. More research needs to be conducted on the long-term clinical outcome of the two methods of treatment, taking into consideration the increased rupture risk with aging and the varying complication rate of the interventional methods based on the bAVM morphology.

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